REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

A. Claim Amendments.

Claim 33 is requested to be cancelled. Claims 18, 23 and 34 are currently being amended, and Claim 35 is being added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 18, 19, 23, 24, 32, 34 and 35 are now pending in this application. No new matter has been added by the foregoing amendments. The restriction requirement made in the previous Office Action has been made final. Applicant has therefore withdrawn Claims 25-31. The amendment to Claim 34 only corrects the dependency in view of the cancellation of Claim 33. In particular, support for the amendments to claims 18 and 23, as well as for new Claim 35, is found in the Specification as follows:

Claim #	Amendment to the Claim	Examples of Specification Support
18, 23	Recites that the dominant negative phospholamban improves cardiac contractility by "...accelerating SERCA2 mediated calcium ion transport in the treated myocytes."	See, e.g., page 11, lines 7-15
18, 23	"a single or double point mutation in Domains I or II" which characterizes a dominant negative phospholamban molecule useful in the invention.	See, e.g., page 3, lines 7-15 (domain structure of phospholamban); page 17, lines 10-20 (point mutations that diminish SERCA2 inhibitory activity).

Claim #	Amendment to the Claim	Examples of Specification Support
35	Condition treated is congestive heart failure.	See, e.g., original Claim 1.

B. Reference to Related Application.

Regarding the question raised in the Office Action as to priority, the application claims the priority of U.S. Provisional Application No. 60/106718, on which PCT Application PCT/US/1999/025692 is based, and further claims the priority of U.S. Provisional Application No. 60/145,883.

C. Response to Rejection of Claims 18-19, 23-24 and 32-34 Under Section 112, First Paragraph (Enablement).

The claims are rejected for lack of enablement on the asserted basis that "[t]he role of...dnPLBs viral vectors in treating a condition associated with the loss of cardiac muscle contractility *in vivo* varies depending on the route of administration, the dose of the vector and cardiac muscle tissue target specificity and the specification does not provide sufficient guidance to address these issues for an artisan to practice the claimed invention." (Office Action at page 8 to page 9, bridging paragraph). In that respect, the Action suggests that while *in vitro* use of the invention to modulate SERCA2 activity is demonstrated (Action at page 9 to page 10, bridging paragraph), the results do not support claims to the use of "any viral vector" encoding for any "dnPLB transgene." (Action at page 10, second paragraph).

Further, the viability of gene therapy techniques in general is questioned, as a basis for the assertion that the outcomes achievable through use of the invention are unpredictable. In that respect, the Office Action asserts that "the problem has been an inability to deliver genes efficiently and to obtain sustained expression." (Action at page 13, first paragraph).

Applicants respectfully disagree, and submits that closer review of the Specification and art reveals that the teachings of the former enable one of ordinary skill in the art to practice the full scope of the claimed invention.

As to the viability of methods for gene therapy of human disease in general, Applicants submit that they have no obligation to address the prospects for clinical success in gene therapy of any condition other than that which they claim to treat. Moreover, Applicants need not prove the efficacy of even the claimed methods, but only that they have enabled their use to an extent sufficient to meet the requisites of 35 U.S.C. §112, first paragraph. As the Federal Circuit advises:

> The commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption...Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas...

In re Brana, 34 U.S.P.Q.2d 1436, 1442-1443 (Fed.Cir. 1995).

The papers relied upon in the Office Action in support of the contention that gene therapy is unpredictable (e.g., Verma) are limited in their conclusions to the issue of whether gene therapy is ready for routine practice in medicine (Verma at p. 239). This is the concern which the *In re Brana* court found to be beyond the proper scope of consideration during patent prosecution. Moreover, Verma does not address the prospects for gene therapy of the heart in general, or of CHF in particular, and therefore is not sufficient to establish that the invention as claimed has not been enabled.

In the context of the invention, the assertion that gene therapy is an unpredictable art because the transfection efficiency and duration of expression achievable with a given construct can vary is not compelling. As to expression, only transient expression of a therapeutic transgene is required to produce a beneficial effect on SERCA2-mediated calcium transients in cardiac myocytes (Giordano, *et al.,* "Intracoronary gene transfer of fibroblast growth factor-5 increases blood flow and contractile function in an ischemic region of the heart," *Nature Medicine*, 2:534-539, 1996, enclosed). Therefore, expression in cardiac myocytes achievable using the methods of the invention, whether transient or longer, should suffice to produce a therapeutic benefit.

As to transfection efficiency, it is well-known in the art that one advantage offered by certain viral vectors is the relatively high transfection efficiency they can achieve (see, e.g., Verma and Weitzman, "Gene therapy: twenty-first century medicine," *Annu.Review Biochem.*, 74:711-738, at 719 (2005) (review article regarding gene therapy vectors, in particular adenoviral and adeno-associated viral vectors) and Sakoda, *et al.,* "A high-titer lentiviral production system mediates efficient transduction of differentiated cells including beating cardiac myocytes," *J.Mol.Cell.Cardio.*, 31(11):2037-47 (1999); references enclosed). Those of ordinary skill in the art would therefore recognize the suitability of the viral vectors presently taught for use in the methods of the invention and be able to construct them without undue experimentation.

Regarding the particular molecules whose use is embraced by the present claims, the claims are now directed to use of phospholamban molecules with single or double point mutations in particular domains of the molecule whose secondary and tertiary structural characteristics are well known. Without conceding that the scope of enablement is limited to the molecules thus claimed, Applicant submits that the task of determining the identity of particular mutations within the specific domains that will achieve the desired function is clearly within the skill of the ordinary artisan to undertake without undue experimentation. This is especially true given the mutations disclosed in the Specification, and the assay means for identification of others taught at pages 25-27 thereof.

As to the nature of the conditions to be treated using the methods of the invention, those of ordinary skill in the clinical arts will be familiar with, or can readily ascertain, which medical conditions are associated with "loss of cardiac muscle contractility," as now claimed. Congestive heart failure is, of course, one such condition, but any loss of contractility can be addressed using the method of the invention. Therefore, restricting the claims to use to treat one condition only would be an undue restriction on the true scope of the invention.

Reconsideration and withdrawal of the rejection of the claims for lack of enablement is therefore respectfully requested.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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